Paget's Disease of Bone: Evidence for Complex Pathogenetic Interactions

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Objectives: Paget's disease of bone (PDB), with a prevalence of 2 to 5% in Caucasians >55 years, is the second most frequent metabolic bone disease, after osteoporosis. PDB characteristics are bone lesions with an imbalanced bone remodeling, resulting in disorganized and nonfully fledged new bone. PDB etiology is not completely understood. In this review, current views on the etiology, clinical aspects, and PDB treatment are summarized and discussed.
Methods: The PubMed database was searched using the keywords PDB, sequestosome1 (SQSTM1), valosin-containing protein (VCP), receptor activator of nuclear factor-κB (RANK), osteoprotegerin (OPG), RANK ligand (RANKL), mutation, genetic variants, virus, osteosarcoma, bisphosphonates, and denosumab.
Results: Environmental evidence (e.g. viruses) and also genetic risk factors have been found for PDB. Until now, *SQSTM1* was the only PDB-causing gene identified. However, PDB patients without *SQSTM1* mutations seem to have susceptibility genetic polymorphisms in regions containing the *CaSR*, *ESR1*, *TNFRSF11B* (OPG), *TNFRSF11A* (RANK), *CSF1* (M-CSF), *OPTN*, *TM7SF4* (DC-STAMP), *VCP*, *NUP205*, *RIN3*, *PML*, and *GOLGA6A* genes, resulting in an increased risk of developing PDB. The nature of these genes indicates that the regulation of osteoclastogenesis is a key process in PDB pathogenesis. Furthermore, with the involvement of SQSTM1 and VCP in autophagy and in forming protein aggregates, this might also indicate that a disturbance of these processes might be a risk factor.
Conclusions: Unraveling the PDB genetic background is instrumental to understanding the PDB pathogenesis and the role of slow viruses. Furthermore, it might make early detection and subsequently treatment of risk individuals possible.
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Bone is a highly organized and complex tissue in the human body. It has a variety of functions: protection of organs; anchor points for muscles, tendons, and ligaments; storage for minerals; and a reservoir for a broad range of cells such as stem cells of the mesenchymal and hematopoietic cell lineages. The bone tissue is continuously remodeled to preserve mineral homeostasis and to maintain its robustness, with the help of a cell orchestra as the main players: the bone-resorbing osteoclasts, the bone-forming osteoblasts, and a signaling network of osteocytes. During remodeling, the damaged or old bone is resorbed by osteoclasts. Then, osteoblasts migrate to this resorbed area to form new bone. Although the newly formed bone is mineralized by osteoblasts, some osteoblasts are entrapped in this newly mineralized bone matrix. These cells are called osteocytes, able to sense the fluctuations in mechanical loading, in hormone levels, etc, forming a large signaling network to communicate with each other, lining cells on the bone surface and with bone marrow stromal cells.

In normal circumstances, bone remodeling is balanced by the interplay of the cells mentioned, through stimuli such as growth factors, hormones, and cytokines. When the bone remodeling is unbalanced, bone diseases can develop, ranging from mild to severe. Osteoporosis is the best known example in which the bone resorbing process

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exceeds the bone formation process. When the balance goes rather towards the bone formation process, this can result in sclerosing bone dysplasias such as osteopetrosis, Van Buchem disease, and Camurati-Engelmann disease. Defects causing both disturbed bone resorption and formation processes arise in several metabolic bone diseases. Among these, the most frequent is Paget's disease of bone (PDB) but there are also a number of rare conditions showing similarities to PDB. These include familial expansile osteolysis (FEO), expansile skeletal hyperphosphatasia (ESH), early-onset PDB (eoPDB), juvenile PDB (JPD), and a syndromal PDB condition named "inclusion body myopathy combined with PDB and frontotemporal dementia" (IBMPFD). These conditions have been very instrumental for genetic research and also for PDB, forming the focus of this review. The aim of this review is to summarize the most recent findings in the research field of PDB (e.g. the discovery of PDB-susceptibility variants and animal models for PDB), and the latest developments in the treating of PDB.

METHODS

We performed an extensive search in the English literature in the PubMed database using the keywords: Paget's disease of bone, familial expansile osteolysis, expansile skeletal hyperphosphatasia, early-onset Paget's disease of bone, juvenile Paget's disease of bone, IBMPFD, SQSTM1, p62, VCP, RANK, TNFRSF11A, OPG, TNFRSF11B, RANKL, TNFSF11, mutation, genetic variants, virus, paramyxovirus, arsenic acid, osteosarcoma, bisphosphonates, denosumab.

RESULTS

PDB-Like Diseases: A Tool in Elucidating the Pathogenesis of PDB

PDB

PDB (MIM no. 602080) was first described by Sir James Paget in the 19th century as "osteitis deformans," as he considered it a chronic inflammation of bone resulting in deformities (1). It is, after osteoporosis, the second most common metabolic bone disease with a prevalence of 2% to 5% in Caucasians over 55 years old (2-10). The disease occurs rarely in other parts of the world (i.e. Africa, Middle East, and Asia) (11-23), unless after migration and integration of a risk population such as the massive British migration to Australia (3,24) and the French acquisition movement to North America (3,25,26). The PDB distribution between men and women is shifted slightly to the men.

In the clinic, many PDB patients are diagnosed incidentally, because PDB is asymptomatic in up to 80% of the cases (27,28). In this case, the PDB diagnosis is found when the patients were examined for other reasons. On bone scan using radionuclide-labeled bisphosphonates or on radiologic film with dual emission radiograph absorption, the characteristic focal bone lesions with accelerated bone turnover can be detected. The accelerated bone turnover results in 3 phases of PDB. First, the increased bone resorption gives an osteolytic appearance, followed by a mixed osteolytic and sclerotic feature in the second phase. Finally, this process leaves a highly sclerotic mark in the affected bone, resulting in a disorganised bone appearance named "woven bone" or "cotton-like bone." These lesions are localized mainly in the axial bone axis and occur in either 1 bone (mono-ostotic) or multiple bones (poly-ostotic). Once a lesion is formed, new lesions rarely develop. The most affected bones are pelvis, femur, (lumbar) spine, skull, tibia, and, to a lesser extent, knee, elbow, phalanges, and calcaneus (29). The lesions are in most cases highly vascular, leading to redness and warmth on the skin surface of the affected site. Histologically, the primary affected cells are osteoclasts that are numerous, enlarged, hypermultinucleated, and hyperactive probably because of the hypersensitivity of RANKL (receptor activator of nuclear factor-κB ligand), 1,25–$(OH)_2D_3$ (1,25–dihydroxyvitamin D_3), and $TAF_{II}17$ (TATA-binding protein–associated factor [17 kDa], a vitamin D receptor binding protein) (30-33). Also, nuclear and cytoplasmatic inclusion bodies can be found in Pagetic osteoclasts (34-38). Biochemical changes involve elevated levels of bone resorption markers (urinary hydroxyproline, serum N-telopeptide of type I collagen, serum C-telopeptide of type I collagen, serum deoxypyridinoline cross-links of type I collagen), and increased levels of bone formation markers (serum alkaline phosphatase [AP], serum bone-specific AP, osteocalcin, serum N-terminal propeptide of type I collagen) (39). Among these biochemical markers, the AP levels are the most important in clinical practice. Complications can develop in PDB patients, for instance, fractures, bone pain, secondary osteoarthritis, deafness, spinal stenosis, and nerve compression syndromes. Heart failure may occur due to the increased blood flow during active PDB, leading to death of the patient. Osteosarcoma is very rare in PDB, affecting approximately 1% of the PDB patients, and the prognosis is very poor (28,29,40). When investigating the quality of life (QOL) between PDB patients and the general population, PDB patients had a slightly reduced mental summary score (48.7 $\pm$ 11.8) than healthy individuals, with the normal population score of 50 in the PRISM (Paget's Disease: a Randomized Trial of Intensive versus Symptomatic Management) study that examined the QOL of 1324 PDB patients using the Short Form-36 (SF-36) questionnaire. However, they had a significantly reduced physical summary score (36.3 $\pm$ 11.3) in comparison with the population normal value of 50, suggesting 3 negative predictors (obtained from a multivariate analysis): PDB-related bone pain, increasing age, and previous bisphosphonates therapy (41). Another QOL study that investigated 285 PDB patients using the SF-12 questionnaire, a shortened form of the SF-36, showed a mean physical component score of 40, consistent with the PRISM study. However,